

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 02/057274 A1

(51) International Patent Classification⁷: C07F 5/02, C07D 207/34
SAMBASIVAM, Ganesh [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore 561 229 (IN).

(21) International Application Number: PCT/IN01/00114
(22) International Filing Date: 14 June 2001 (14.06.2001)
(25) Filing Language: English
(26) Publication Language: English
(30) Priority Data:
PCT/IN01/00006 19 January 2001 (19.01.2001) IN

(71) Applicant (for all designated States except US): BIOCON INDIA LIMITED [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore 561 229 (IN).

(72) Inventors; and
(75) Inventors/Applicants (for US only): SRINATH, Sumitra [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore 561 229 (IN). MATHEW, Joy [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore 561 229 (IN). UJIRE, Sandhya [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore 561 229 (IN). SRIDHARAN, Madhavan [IN/IN]; 20th Km Hosur Road, Hebbagodi, Bangalore 561 229 (IN).

(74) Agents: ANAND, Pravin et al.; Anand & Anand Advocates, B-41, Nizamuddin East, New Delhi 110 013 (IN).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 02/057274 A1

(54) Title: A PROCESS FOR THE SYNTHESIS OF ATORVASTATIN FORM V AND PHENYLBORONATES AS INTERMEDIATE COMPOUNDS

(57) Abstract: The present invention discusses a novel process for the synthesis of [R-(R*,R*)]-2-(4-fluorophenyl)-B,D-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium, atorvastatin form V. The compound so prepared is useful as inhibitors of the enzyme HMG-CoA reductase and are thus used as hypolipidemic and hypocholesterolemic agents.

PC25825A
APP. NO. 10/828,488 FILED: 04/20/2004

A PROCESS FOR THE SYNTHESIS OF ATORVASTATIN FORM V AND PHENYLBORONATES AS
INTERMEDIATE COMPOUNDS

FIELD OF THE INVENTION:

This invention relates to a process for manufacturing R-(R*,R*)]-2-(4-fluorophenyl)-B,D-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt, atorvastatin form V and the novel intermediates produced during the course of manufacture. The said compound is useful as inhibitors of the enzyme HMG-CoA reductase and are thus useful as hypolipidemic and hypocholesterolemic agents.

10

BACKGROUND OF THE INVENTION

US Patent No. 4,681,893, discloses a route using resolution of the racemic product using R (+) α -methyl benzyl amine. US patent No. 5,003,080 discloses a synthetic route for the preparation of the chiral form of atorvastatin. The patent discloses a process for the preparation of the lactone or its salts by coupling an ester of (4R)-6-(2-aminoethyl)-2,2-dialkyl-1,3-dioxane-3-acetate with 4-fluoro- α -[2-methyl-1-oxopropyl] γ -oxo-N- β -diphenylbenzenebutaneamide followed by deprotection and hydrolysis to give the product. The product suffers from the fact ozonolysis is required as one of the steps for the synthesis of the amino ketal intermediate, which is hazardous for large scale preparation.

15 The patent describes an alternate procedure wherein 4-fluoro- α -[2-methyl-1-oxopropyl] γ -oxo-N- β -diphenylbenzenebutaneamide is reacted with 3-amino propinaldehyde acetal followed by conventional procedures to give atorvastatin.

20

US patent No. 5,216,174, No. 5,097,045, No. 5,103,024, No. 5,124,482, No. 5,149,837, No. 5,155,251, No. 5,216,174, No. 5,245,047, No. 5,273,995, No. 5,248,793, and No. 5,397,792 describes various minor modifications in the procedure for the preparation of atorvastatin calcium salt.

25 Synthesis of esters of (4R)-6-(2-aminoethyl)-2,2-dialkyl-1,3-dioxane-3-acetate is an important part of the preparation of atorvastatin calcium. US patent 5,155,251 also discloses a synthetic route for the synthesis of (3R)-4-cyano-3-hydroxy butyric acid esters from (S)-3-hydroxy butyrolactone, which in turn is synthesized from a suitable carbohydrate substrate.

Other patents like 5,292,939, 5,319,110 and 5,374,773 discloses the preparation of 3,4-dihydroxybutyric acid. However, isolation of this highly water soluble compound or its lactone is not attempted.

Another multi step procedure starting from (S)-malic acid (J. org. Chem., 1981, 46, 5 4319) is reported. Esters of (S)-malic acid have also been used (Chem. Lett., 1984, 1389) for the synthesis of the hydroxy lactone involving BMS-NaBH₄ reduction, followed by lactonization. While a six step procedure from D-isoascorbic acid is also reported (Syn., 1987, 570) but this process requires a silica gel chromatographic separation of the diasteromeric mixtures.

10 Optical resolution of the racemic hydroxylactones using lipase is disclosed in US patent 5,084,392 but this method suffers from poor enantiomeric excess and loss of the other active isomer.

15 Thus, these prior art procedures involves cumbersome reaction conditions or expensive starting materials, reagents which are difficult to handle or hazardous for scale up, coupled with a multi step procedure which results in poor overall yield.

The object of the present invention is to disclose an inexpensive, simple and scalable route for the synthesis of atorvastatin form V. PCT pending application filed on March 28, 2000 (PCT/IN00/00030) discloses a process for the synthesis but uses a different amino acid fragment for the condensation reaction to get atorvastatin calcium.

20 Reference is also made to co-pending application filed on January 19, 2001 (PCT/IN01/00006) claims the form V polymorph of atorvastatin calcium.

DETAILED DESCRIPTION OF THE INVENTION

25 The process of the present invention in its first aspect is a new, improved, economical, and commercially feasible method for preparing HMG CoA reductase inhibitors of Formula XII which are useful as inhibitors of the enzyme HMG CoA reductase and are thus useful as hypolipidemic or hypocholesterolemic agents is outlined in Scheme 1 - 4.

Structure XII.

30 Accordingly, the present invention provides a process for the synthesis of Atorvastatin Form V (formula XII) which comprising:

a) reacting of compound of formula X with a compound of structure IV in a mixture of solvents chosen from xylene, cyclohexane, methyl tert-butyl ether,

diisopropyl ethyer, acetonitrile, in the presence of a catalyst chosen from pivalic acid, trifluoromethyl sulfonic acid, methane sulfonic acid or p-toluene sulfonic acid, to give an intermediate of structure XI,

5 b) hydrolysis of the compound of structure XI followed by calcium salt formation,

c) the crude calcium salt is isolated as Form V.

Compound of Formula X used in step (a) where R is selected from C_6H_5 or substituted phenyls is prepared by:

i) reacting a compound of formula V with dihydro pyran to give a protected ether of formula VI.

ii) reacting a compound of formula VI with tert-butyl acetate with a base at -30 to -80°C to give a compound of formula VII.

iii) reducing a compound of formula VII to give a compound of formula VIII,

iv) converting a compound of formula VIII to a protected boraonate ester of formula IX,

v) reducing a compound of formula IX to give a compound of formula X.

The reducing agent used in step (c) is selected from zinc borohydride, The protecting group used in step (d) is selected from phenyl boronic acid, tolyl boronic acid or 3,nitro benzene boronic acid. Form V atorvastatin Calcium and hydrates thereof are

(i) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water

(ii) filtering out not the solid

(iii) drying to get Form V statin calcium

25

The ratio of water and absolute ethanol is in the range of 3:1 to 8:1. The ratio of water and alcohol is 4.67:1. The stirring is carried out at 25 - 50 deg centigrade. The

stirring is carried out at 40 deg centigrade for 10 - 25 hrs. The stirring is carried out for 17 hours. The final product is dried in vacuum tray drier.

An intermediate of formula IX, where R is selected from C_6H_5 or substituted phenyls.

5 An intermediate of formula X, where R is selected from C_6H_5 or substituted phenyls.

An intermediate of formula XI, where R is selected from C_6H_5 or substituted phenyls.

10 The present invention further comprises a pharmaceutical composition comprising of Form V atorvastatin calcium in admixture with at least one pharmaceutically acceptable excipient, diluent or carrier. The pharmaceutical composition is selected from tablets, capsules, powder or lozenges.

15 The present invention also relates to a method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to claims 16-17 in unit dosage form.

The synthetic scheme for the synthesis of the amino ester of formula X is outlined in scheme 1

Scheme - 1

20 Thus, a cyano hydroxyester of formula V is treated with dihydropyran in the presence of p-toluenesulfonic acid in a solvent like, CH_2Cl_2 , CH_3CN , DMF etc., to give the protected ether of formula VI, which is subsequently treated with the anion of tert-butyl acetate generated by reacting tert-butyl acetate with lithium diisopropylamide in THF to give a compound of formula VII.

25 A β -keto ester of formula XII is then reduced using zinc borohydride in THF to give a dihydroxy compound of formula VIII.

The dihydroxy ester compound of formula VIII is then protected using a boronic acid of formula $RB(OH)_2$

30 Where R is chosen from phenyl or substituted phenyl to afford a boronate ester of Formula IX. Preferably, the reaction is carried out with phenyl boronic acid under a nitrogen atmosphere.

A boronate ester of Formula IX is then reduced using Raney Nickel to give the amino ester of formula X.

A amino ester of Formula X is reacted with a diketone of Formula IV wherein the process for the preparation of the compound of formula IV is described in scheme 2.

Scheme – 2

A compound of formula IV is prepared as described in scheme 2, which comprises 5 of reacting isobutyryl chloride and meldrum's acid in the presence of a base chosen from pyridine, triethylamine, diisopropylethyl amine, dimethylaniline etc in CH_2Cl_2 at 0-5°C for about 18h to give an acyl meldrum acid which is then reacted with aniline in a solvent chosen from CH_2Cl_2 , acetonitrile, toluene etc., at the reflux temperature of the solvent for about 12h to afford the amide of formula II. Preferably the reaction is done in pyridine and 10 CH_2Cl_2 at 0°C and in CH_2Cl_2 by stirring at room temperature.

The keto amide of formula II is then reacted with benzaldehyde in the presence of a base chosen from aqueous NaOH, or lithium hydroxide etc., and alumina for about 26h to give the methylenephenoxy intermediate of formula III.

The compound of formula III is treated with 4-fluorobenzaldehyde in the presence 15 of a catalyst chosen from metallic cyanide where the metal is Ag, K, Na, Cu, tetraalkylammonium etc., or trimethylsilyl cyanide in a polar solvent chosen from DMSO, DMF, acetonitrile etc., at the reflux temperature of the solvent to give a compound of formula IV. Preferably the reaction is carried out by reacting 4-fluorobenzaldehyde and sodium cyanide in DMSO at reflux temperature.

20 The diketone of formula IV is reacted with the amino ester of formula X as described in Scheme 3 in the presence of a catalyst of Formula $\text{R}_{12}\text{SO}_3\text{H}$, wherein R_{12} is chosen from CF_3 , CH_3 , $\text{p-CH}_3\text{C}_6\text{H}_4$ and a solvent or mixtures thereof such as, for example, acetonitrile, xylene, diisopropyl ether cyclohexane, methyl tert-butyl ether and the like for about 24 to about 48 hours from 5 to 10°C to about the reflux temperature of the solvent 25 with the removal of water to afford a compound of Formula XI. Preferably, the reaction is carried out in the presence of methanesulfonic acid and a mixture of xylene-hexane at reflux for about 48 hours with the removal of water.

Scheme – 3

30 The compound of formula XI is converted to atorvastatin calcium as shown in scheme 4

Scheme – 4

Which involves the deprotection of the boronate ester followed by hydrolysis of the ester to give the free acid which is converted to its ammonium salt by reacting with either 5 NH_4OH , methanolic NH_3 or by bubbling gaseous NH_3 to the solution of carboxylic acid in a solvent chosen from a mixture of EtOAc , hexane, diisopropyl ether, isopropanol, cyclohexane and methanol. Preferably the intermediate of formula XI is de-protected using aqueous sodium hydroxide at room temperature over a period of 24h and is then hydrolyzed using methanolic sodium hydroxide and acidified using dil HCl to give the free 10 acid which is converted to its ammonium salt by passing gaseous NH_3 in EtOAc . The ammonium salt is then treated with calcium acetate to give atorvastatin calcium.

The invention will now be described with reference to the following examples.

Example 115 **1.1 Preparation of 4-methyl-3-oxo-N-phenylpetanamide (Formula II).**

To a suspension of malonic acid (104g) in acetic anhydride (120mL) at room temperature, Conc. H_2SO_4 (3mL) was added. The mixture was cooled to 20°C followed by the addition of acetone (80mL) drop wise. The contents were stirred at room temperature (15min) and kept at 0-5°C overnight and filtered. The solid was washed with cold water 20 and cold acetone and dried. The crude material was recrystallized from acetone-hexane mixture.

Meldrum's acid (59g) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0°C. Pyridine (73mL) was added drop wise over a period of 30 min and the mixture was stirred for an additional 10 min. Isobutyryl chloride (44g) was added drop wise over a period of 25 30 min. and the mixture was stirred at 0°C for 1h followed by stirring at room temperature over night. The mixture was poured into 1.5N HCl containing crushed ice. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x100mL). The combined extracts were washed with 1.5N HCl (2x100mL) followed by saturated NH_4Cl solution (2x100mL) and dried over Na_2SO_4 and concentrated under reduced pressure to afford the 30 crude acyl meldrum's acid which was used for the next step.

The crude acyl meldrum's acid (84g) was taken in benzene (300mL) and aniline (111mL) was added. The mixture was refluxed for 4h. Cool the reaction mixture to room temperature and wash with 2N HCl (5x100mL) and benzene was removed under reduced pressure to get formula II.

Example 1.2**Preparation of 4-methyl-3-oxo-N-phenyl-2-(phenylmethylene) pentanamide (Formula III).**

The crude amide was added to a slurry of alumina impregnated with lithium hydroxide in tetrahydrofuran. To this mixture at room temperature benzaldehyde was added. The contents were allowed to stir under reflux for 2h. The contents were filtered, tetrahydrofuran was removed under reduced pressure and the residue was extracted with CH₂Cl₂. The organic extracts were washed with bicarbonate, bisulfite solution, dried and concentrated under reduced pressure to afford the crude compound of formula III.

10

Example 1.3**Preparation of 4-fluoro- α -[2-methyl-1-oxopropyl]y-oxo-N- β -diphenylbenzenebutaneamide (Formula IV).**

To 4-fluorobenzaldehyde in anhydrous DMF, sodium cyanide was added and the contents were refluxed for 4h. To this the intermediate from example 3 was added and the contents were stirred for an additional 18h. Usual work up affords the crude diketo compound of formula IV.

Example 1.4**Preparation of 4-cyano-3-(O-tetrahydropyranyl) butyric acid ethyl ester (Formula VI).**

A solution of 50g of 4-cyano-3-hydroxybutyric acid ethyl ester in dichloromethane (1L) and dihydropyran (53.57g) and catalytic quantity of PPTS (15.9g) was stirred at room temperature over a period of 24h. Upon completion, the contents were washed with bicarbonate, dried and solvent was removed under reduced pressure to give the title compound.

Example 1.5**Preparation of tert-butyl 6-cyano-5-hydroxy-3-oxohexanoate (Formula VII).**

To a solution of THF (50mL) and diisopropylamine (37.6ml), b-Butyl lithium (186.5ml) at a temperature of -10°C and maintained at -3°C for 30min. To this solution at -20 to -25°C tertiary butyl acetate (34.97ml) in 35ml of THF was added and the temperature was maintained for 1h. The ether (14g) in 14ml of THF from the above example was added

at -20 to -25°C and maintained for 3h. The contents were quenched with 3N HCl to a pH of 6-7. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with water, brine, dried and concentrated under reduced pressure to give the title compound of formula VII.

5

Example 1.6**Preparation of tert-butyl 6-cyano-3,5-dihydroxyhexanoate (Formula VIII).**

The crude product from the above example was taken up in dry THF and isopropanol under nitrogen atmosphere. The solution was cooled to -10°C and a solution of zinc borohydride was added. The temperature was maintained between -10°C to -15°C and was allowed to warm to room temperature and stand for 18h. The reaction was quenched by addition of acetic acid and concentrated under reduced pressure to afford an oily residue.

15 **Example 1.7****Preparation of (4R)-tert-butyl 6-cyano-3,5-dihydroxy phenylboronato hexanoate (Formula IX).**

To the diol from the above example (10g) was reacted with phenyl boronic acid (5.5g) in toluene. The contents were refluxed for 20h and the water was collected by 20 azetropie distillation. Toluene was removed under reduced pressure and petroleum ether was added to the oily residue was cooled to 0°C to precipitate the solid boronate.

Example 1.8**Preparation of (4R)-tert-butyl 7-amino-3,5-dihydroxy phenylboronato heptanoate (Formula X)**

The boronate ester (5g) from the above example was added to saturated solution of methanolic ammonia and Raney Nickel (5g) was added. The contents were hydrogenated under pressure (5kg). The contents were filtered over celite bed, methanol was removed under reduced pressure to afford the crude title compound of formula X.

30

Example 1.9

Preparation of [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[phenylaminocarbonyl]-1H-pyrrole-1-heptanoic acid, hemi calcium salt (Formula XII)

A solution of (4R)-tert-butyl 7-amino-3,5-dihydroxy phenylboronato heptanoate (Formula X) and 4-fluoro- α -[2-methyl-1-oxopropyl] γ -oxo-N- β -diphenylbenzenebutaneamide (formula IV) and acetic acid in xylene were heated to reflux to 44h. The solution was diluted with diisopropyl ether and methanol and was washed with dilute methanolic sodium hydroxide solution, dilute HCl and the solvent was then removed under vacuum. The crude oil was stirred with moist silica in CH₂Cl₂ and was stirred at room temperature for 18h. A solution of aqueous NaOH was then added at room temperature and was stirred for 4h. The reaction mixture was diluted with water and was washed with diisopropyl ether. The aqueous layer was acidified with HCl and was taken up in diisopropyl ether. The crude acid intermediate was then taken up in EtOAc and NH₃ gas was bubbled. The contents were stirred for completion of the reaction and solvent was removed upon which the product crystallized. The crude ammonium salt is then taken up in diisopropyl ether-isopropanol mixture and a solution of calcium acetate was added at room temperature upon which the calcium salt precipitated from the solution. The product was filtered and dried under vacuum to get formula XII of acceptable pharmaceutical purity.

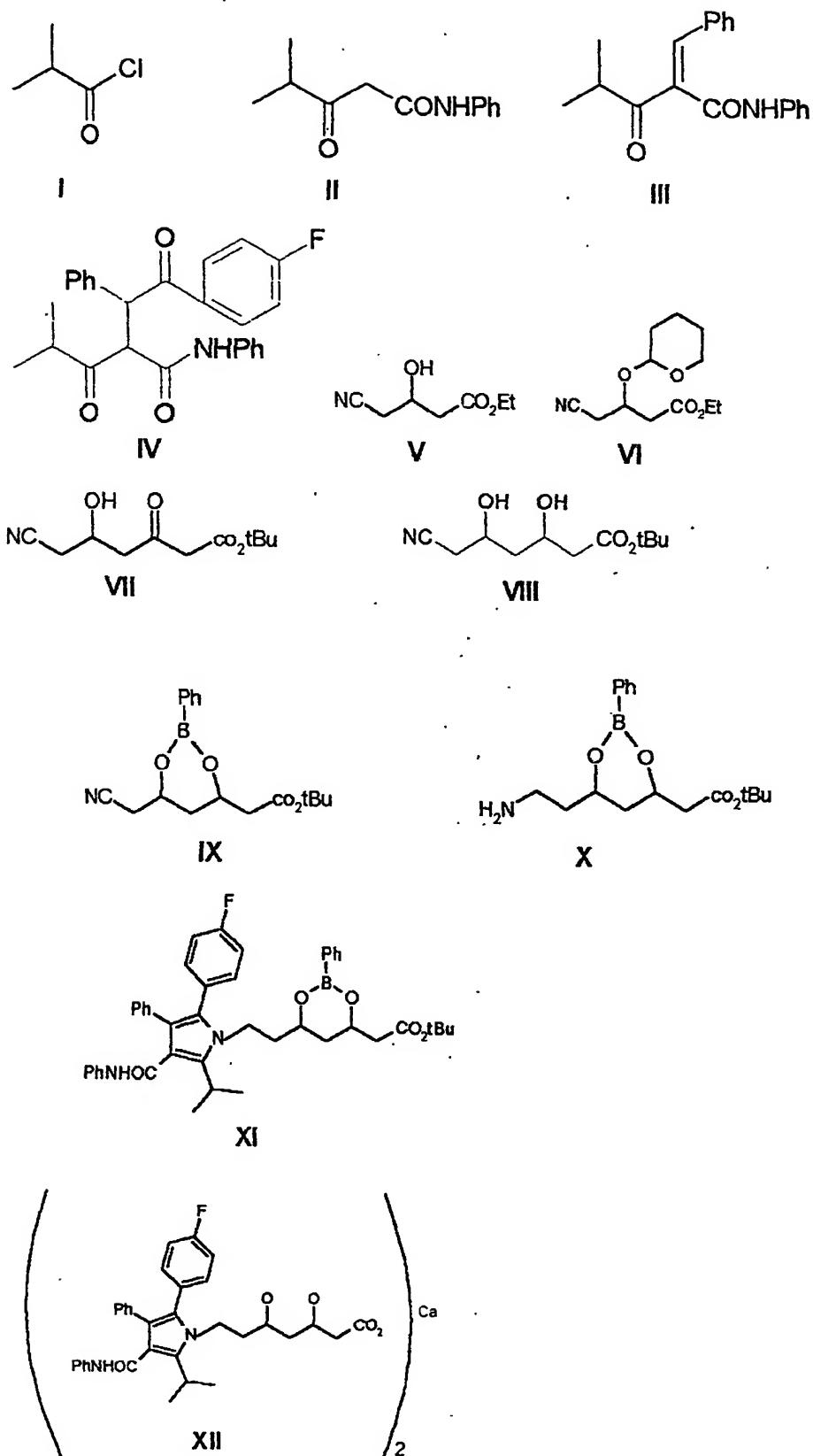
20

Example 1.10

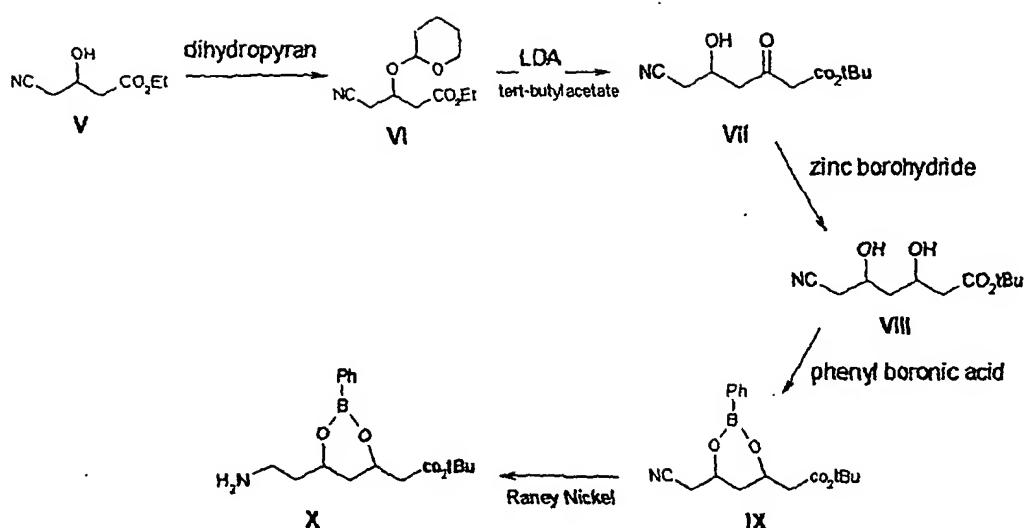
Form V

A heterogeneous mixture of Atorvastatin Calcium (10 g) stirred in a mixture of water and absolute ethanol (140 ml:30 ml respectively) at 40 deg centigrade for 17 hrs. The product is filtered and suck dried. The filtered semi dried product is dried in a vacuum tray drier (650 mm Hg) for 17 hrs. to get 9 g of finished product.

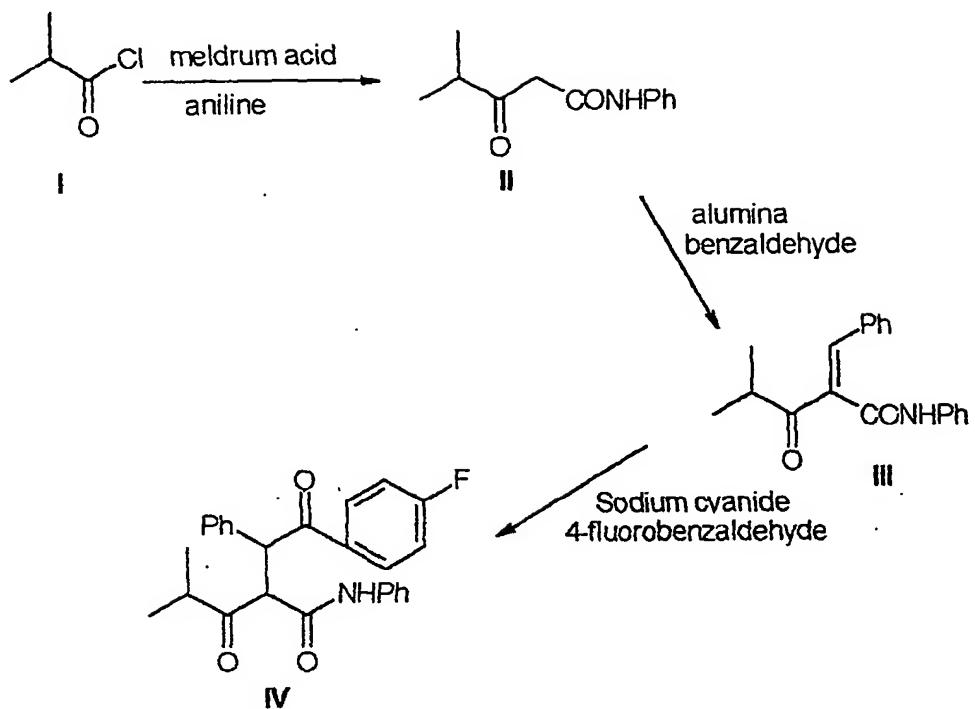
The invention has been described by reference to specific embodiments, this was for the purpose of illustration only. Numerous alternative embodiments will be apparent to those skilled in the art and are considered within the scope of these claims.



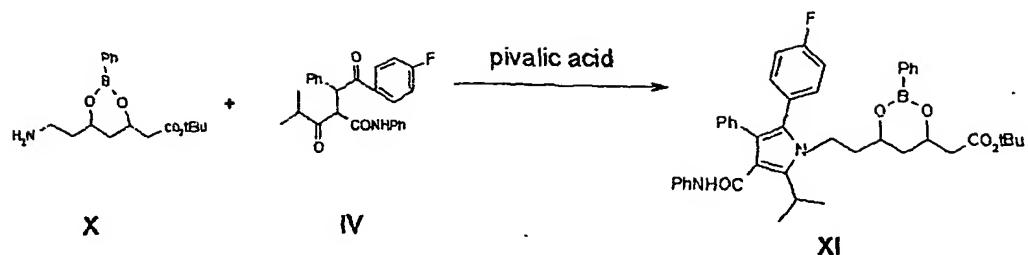
Scheme -1



Scheme – 2

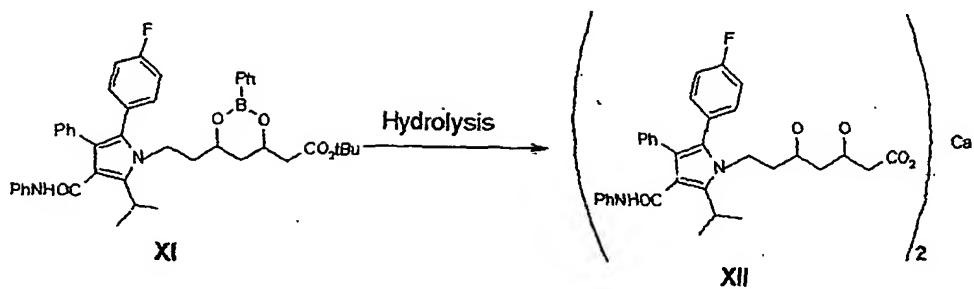


Scheme - 3



5

Scheme - 4



10

13

We claim:

1. A process for the synthesis of Atorvastatin Form V (formula XII) which comprising:

5 a) reacting of compound of formula X with a compound of structure IV in a mixture of solvents chosen from xylene, cyclohexane, methyl tert-butyl ether, diisopropyl ether, acetonitrile, in the presence of a catalyst chosen from pivalic acid, trifluoromethyl sulfonic acid, methane sulfonic acid or p-toluene sulfonic acid, to give an intermediate of structure XI,

10 b) hydrolysis of the compound of structure XI followed by calcium salt formation,
c) the crude calcium salt is isolated as Form V.

2. A process as claimed in claim 1 wherein compound of Formula X used in step (a) where R is selected from C_6H_5 or substituted phenyls is prepared by:

15 i) reacting a compound of formula V with dihydro pyran to give a protected ether of formula VI,
ii) reacting a compound of formula VI with tert-butyl acetate with a base at -30 to -80°C to give a compound of formula VII,
iii) reducing a compound of formula VII to give a compound of formula VIII,
iv) converting a compound of formula VIII to a protected boraonate ester of formula IX,
20 v) reducing a compound of formula IX to give a compound of formula X.

3. The process as claimed in claim 2, wherein the reducing agent used in step (c) is selected from zinc borohydride,

4. The process as claimed in claim 2, wherein the protecting group used in step (d) is selected from phenyl boronic acid, tolyl boronic acid or 3,nitro benzene boronic acid.

25 5. The process as claimed in claim 1, wherein Form V atorvastatin Calcium and hydrates thereof are isolate in step (c) by :

- (i) stirring heterogeneous mixture of atorvastatin calcium in a mixture of water and absolute ethanol;
- (ii) filtering to get the solid;
- (iii) drying to get Form V atorvastatin calcium.

5

6. A process as claimed in claim 5 wherein the ratio of water and absolute ethanol is in the range of 3:1 to 8 :1.

10

7. A process as claimed in claim 6, wherein the ratio of water and alcohol is 4.67: 1.

15

8. A process as claimed in claim 5, wherein the stirring is carried out at 25 - 50 deg centigrade.

15

9. A process as claimed in claim 8, wherein the stirring is carried out at 40 deg centigrade.

20

10. A process as claimed in claim 5, wherein the stirring is carried out for 10 - 25 hrs.

25

11. A process as claimed in claim 10, wherein the stirring is carried out for 17 hours.

20

12. A process as claimed in claim 5, wherein the final product is dried in vacuum tray drier.

25

13. The intermediate of formula IX, where R is selected from C₆H₅ or substituted phenyls.

14. The intermediate of formula X, where R is selected from C₆H₅ or substituted phenyls.

30

15. The intermediate of formula XI, where R is selected from C₆H₅ or substituted phenyls.

16. A pharmaceutical composition comprising of Form V atorvastatin calcium in admixture with at least one pharmaceutically acceptable excipient, diluent or carrier.

17. The pharmaceutical composition as claimed in claim 16, is selected from tablets, capsule, powder or lozenges.
18. A method of treating hyperlipidemia and hypercholesterolemia comprising administering to a host suffering therefrom a therapeutically effective amount of a compound according to claims 16-17 in unit dosage form.
5

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/IN 01/00114

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F5/02 C07D207/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 68221 A (EGYT GYOGYSZERVEGYESZETI GYAR ;VERECZKEYNE DONATH GYOERGYI (HU); B) 16 November 2000 (2000-11-16) page 1 -page 2 ---	16-18
A	US 5 155 251 A (BUTLER DONALD E ET AL) 13 October 1992 (1992-10-13) cited in the application Scheme 1 examples 2,3,5 ---	1-15
A	US 5 397 792 A (BUTLER DONALD E ET AL) 14 March 1995 (1995-03-14) cited in the application Scheme 1 ---	1-15

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

5 March 2002

12/03/2002

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Von Daacke, A

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/IN 01/00114

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 cited in the application the whole document -----	1-15

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/IN 01/00114

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0068221	A	16-11-2000	HU AU EP WO	9901526 A2 4600200 A 1178980 A1 0068221 A1	28-04-2001 21-11-2000 13-02-2002 16-11-2000
US 5155251	A	13-10-1992	AT AU AU CA DE DE DK EP ES FI JP JP MX NO PT SG WO ZA	175190 T 667320 B2 2764192 A 2116973 A1 69228073 D1 69228073 T2 643689 T3 0643689 A1 2129457 T3 941632 A 7500105 T 3241723 B2 9205824 A1 941280 A 100943 A , B 46599 A1 9307115 A1 9207793 A	15-01-1999 21-03-1996 03-05-1993 15-04-1993 11-02-1999 10-06-1999 30-08-1999 22-03-1995 16-06-1999 08-04-1994 05-01-1995 25-12-2001 01-04-1993 08-04-1994 29-10-1993 20-02-1998 15-04-1993 11-04-1994
US 5397792	A	14-03-1995	US US US US US US US AT AU AU CA CZ CZ CZ CZ CZ DE DE DK EP ES FI GR HU JP NO NO NO NZ RU SK SK WO	5342952 A 5298627 A 5446054 A 5470981 A 5510488 A 5489691 A 5489690 A 156127 T 677047 B2 6274294 A 2155952 A1 285554 B6 285555 B6 9800479 A3 9502206 A3 69404632 D1 69404632 T2 687263 T3 0687263 A1 2108435 T3 954073 A 3024784 T3 75034 A2 8507521 T 953438 A 994708 A 20000910 A 262830 A 2138497 C1 109095 A3 281110 B6 9420492 A1	30-08-1994 29-03-1994 29-08-1995 28-11-1995 23-04-1996 06-02-1996 06-02-1996 15-08-1997 10-04-1997 26-09-1994 15-09-1994 15-09-1999 15-09-1999 11-08-1999 13-12-1995 04-09-1997 29-01-1998 16-02-1998 20-12-1995 16-12-1997 30-08-1995 30-01-1998 28-03-1997 13-08-1996 01-11-1995 22-11-1999 13-03-2000 26-11-1996 27-09-1999 06-12-1995 11-12-2000 15-09-1994